REMARKS

Claims 75, and 77-112 are presently pending and new claims 113 to 133 have been added. Claims 75, 77, 81-85, 98, and 99 have been amended. The amendment to the claims is supported by the specification and do not add new matter.[1] Moreover, the new claims are supported by the specification and do not add new matter.[2] The applicants respectfully request the examiner to consider the following remarks in light of the presently pending claims.

I. 35. U.S.C. §112, Second Paragraph Rejections

Reconsideration is respectfully requested of the rejection of claim 75-104 under 35 U.S.C. § 112, second paragraph. The Office has rejected the claims as indefinite because of the recitation of the phrase "an acceptable diluent, adjuvant, or excipient." Per the claim amendments, this phrase has been deleted. In view of the amendment, claims 75-104 are definite, and the rejection is moot.

Claims 75, 96, and 97 were also rejected as indefinite because the term "subject," per the Office, is not clearly defined. These claims have been amended to replace "subject" with "food or water." In view of this amendment, claims 75, 96, and 97 are definite, and the rejection is moot.

II. 35. U.S.C. § 102 Rejection

Reconsideration is requested of the rejection of claims 75-80, 82-85, 90, 92-93, and 104 under 35 U.S.C. §102 (b) in view of U.S. Patent No. 5,928,686 ('686 patent) and as evidenced by U.S. Patent No. 2,938,053 ('053 patent).

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[1] Support for the amendments to claims 75, 98, and 99 may be found at page 14, paragraph 557; at page 16, paragraph 591; and at page 18, paragraph 601. The amendment to claims 77, and 81-85 merely correct claim dependency.

[2] Support for claim 113 may be found on page 12, paragraph 542. Support for claims 114 to 117 may be found on page 13, paragraph 549 and in the Examples. Support for claims 118 to 120 may be found in claims 18 to 20. Support for claims 121 to 123 may be found in claims 23 to 25. Support for claims 124 to 126 may be found in claims 29 to 31. Support for claims 127 to 129 may be found in claims 32 to 34. Support for claims 130 to 132 may be found in claims 35 to 37. Support for claim 133 may be found on page 14, paragraph 558.

Amended claim 75 is directed to a method of killing microbes in food or water. The method comprises treating the food or water with an antimicrobial composition. The antimicrobial composition comprises **at least two organic acids** selected from the group **consisting of** formic acid, butyric acid, fumaric acid, lactic acid, benzoic acid, and propionic acid; and a third organic acid that is a compound of formula (I). As such, minimally claim 75 requires the combination of at least three different organic acids.

The '686 patent discloses a feed ration that among other ingredients has Alimet® (i.e., 2-hydroxy-4-(methylthio)butanoic acid), propionic acid, and citric acid.[3] The '053 patent discloses that 2-hydroxy-4-(methylthio)butanoic acid has antimicrobial activity.[4] Nowhere do either the '686 patent or the '053 patent disclose or suggest an antimicrobial composition that comprises **at least two organic acids** selected from the group **consisting of** formic acid, butyric acid, fumaric acid, lactic acid, benzoic acid, and propionic acid; and a compound of formula (I), as required by each of claims 75-80, 82-85, 90, 92-93, and 104. Because the cited art does not disclose all of the recited elements of claims 75-80, 82-85, 90, 92-93, and 104, neither 'the 686 patent nor the '053 patent anticipates the aforementioned claims.

In view of the foregoing, the Applicants respectfully request withdrawal of the §102 (b) rejections of claims 75-80, 82-85, 90, 92-93, and 104 in view of either the '686 patent or the '053 patent.

III. 35. U.S.C. § 103 Rejections

For the reasons detailed below, all pending claims are not rendered obvious by any single reference, or combination of references cited by the Office.

[3] '686 patent at column 7.
[4] '053 patent at column 1.

(a) Claims 75-82, and 96 are not rendered obvious by Paquet et al.

Reconsideration is requested of the rejection of claims 75-82, and 96 under 35 U.S.C. 103 (a) in view of Paquet et al.[5]

Three criteria must be present to establish a *prima facie* case of obviousness.[6] First, the prior art reference must teach or suggest all the claim limitations. Second, there must be some suggestion or motivation in the knowledge generally available to one of ordinary skill in the art to modify the reference. Third, there must be a reasonable expectation of success.[7] Not one of these three criteria is satisfied by Paquet al.

Paquet et al. is asserted by the Office to disclose that N-acyl-D methionine (i.e., a compound that is said to read on Formula I) has antimicrobial activity, and that sorbic acid has antimicrobial activity. Further, per the Office, both compounds are used in the preservation of food. Even assuming, *arguendo*, that the cited art discloses every feature the Office claims it does—a *prima facie case* of obviousness has not been established.

While acknowledging that sorbic acid has antimicrobial activity, Paquet et al. **teaches away** from its use in the preservation of food and water. Specifically, Paquet et al teaches that sorbic acid can have undesired **mutagenic effects** and is therefore undesirable as an antimicrobial agent. As recited by the reference, "[R]ecent reports show that mutagenicity was detected in some food preparations cured with the sorbic acid-sodium nitrite mixtures. Reports on mutagenicity of sorbic acid itself in win and curing brines have also emerged. There is, therefore a need for the preservatives, which do not have these side effects. (internal citations omitted). " See Paquet et al, pg. 3.

In addition, Paquet et al. fails to suggest or teach any combination of organic acids for use in the preservation of food and water. Importantly, the recitation of a general N-acylamino acid formula does not teach or suggest any combination of distinct organic acids.

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[5] Paquet et al., CA Patent No. 1261855.
[6] MPEP §2143.
[7] *Id.*

Even assuming, *arguendo*, that the cited art does not have the detailed failings described above—a *prima facie case* of obviousness still has not been established. Simply put, Paquet et al. does not teach or suggest all the limitations of claim 75. Claim 75 requires use of an antimicrobial composition to inhibit microbe growth in food or water. The antimicrobial composition, per claim 75, **requires at least two organic acids** selected from the group **consisting of formic acid, butyric acid, fumaric acid, lactic acid, benzoic acid, and propionic acid**; and a compound of formula (I). The cited art does not disclose or suggest a combination of at least three organic acids, as required by claim 75. In this context, Paquet et al. does not disclose or suggest an antimicrobial composition that has at least two organic acids from the recited list in combination with a compound of formula (I). Importantly, claim 75 does not require sorbic acid or a combination of sorbic acid and a compound of formula (I).

Because Paquet el al. do not disclose the claimed antimicrobial composition or provide any motivation for one skilled in the art to modify that which is disclosed to the antimicrobial composition of Claim 75, Applicants respectfully submit that claim 75 is patentable over Paquet et al. Each of claims 77-82, and 96 require the antimicrobial composition of claim 75, and therefore, are each likewise patentable over Paquet et al.

(b) Claims 99-103 are not rendered obvious by the cited art

Reconsideration is requested of the rejection of claims 99-103 under 35 U.S.C. 103 (a) in view of Doerr et al.[8] and Rolow et al. ('289 patent)[9].

Doerr et al. is said to disclose killing mold in ground corn by treating it with hydroxyl-methylthio butanoic acid. Rolow is asserted by the Office to disclose extending the shelf life of tortillas made from corn by adding mold inhibitors "such as propionic acid." If the cited art discloses every feature the Office purports it does—a *prima facie case* of obviousness has not been established.

[8] Doerr et al., Poultry Science, 74(1), page 23.
[9] U.S. Patent 6,355,289.

Doerr et al. and Rolow et al.—when taken singly or collectively—do not teach or suggest all the limitations of claim 99. Claim 99 requires use of an antimicrobial composition to inhibit mold growth in food having a moisture content of from 0% to 17%. The antimicrobial composition, per claim 99, **requires at least two organic acids** selected from the group **consisting of** formic acid, butyric acid, fumaric acid, lactic acid, benzoic acid, and propionic acid; and a third organic acid that is a compound of formula (I). The cited art does not disclose or suggest an antimicrobial composition that has at least two organic acids from the recited list in combination with a third organic acid that is a compound of formula (I). Simply put, each cited reference suggests use of a single organic acid and neither suggests their combination. Even if the references are combined, they do not disclose the use of three organic acids in combination, as required by claim 99.

In support of its obviousness position, the Office cites *In re Kerkhoven*.[10] *Kerkhoven*, however, is distinguishable from the presently claimed invention. In *Kerkhoven*, the issue was whether the claimed process for the production of particulate detergent compositions containing a mixture of anionic and nonionic active detergent materials was patentable. The CCPA held that is was not, and, in so deciding stated "[i]t is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose."[11]

As an initial matter, both Doerr et al and Rolow et al. fail to establish that a compound of formula (I) has any antimicrobial activity. Importantly, *In re Kerkhoven* cannot be applied unless the compound of formula (I) has known antimicrobial activity. Absent some objective proof or showing, one of ordinary skill in the art cannot assume that the compound of formula (I) would necessarily provide antimicrobial activity by itself. As such, Examiner has failed to provide any showing by Doerr et al. or Rolow et al. to establish antimicrobial activity of a

[10] *In re Kerkhoven*, 626 F.2d 848, 205 USPQ 1069 (CCPA 1980).
[11] *Id.* 626 F.2d. at 850, 205 USPQ at 1072.

compound of formula (I). Because Doerr et al. and Rolow et al. do not provide a description of function for the compound of formula (I), there is also no motivation to combine and no reasonable expectation of success indicated by the prior art, as required by Section 103.

Further, the instant situation involving claim 99 and the disclosure of Doerr et al. and Rolow et al. is distinguishable from the facts of *Kerkhoven*. In particular, every organic acid may potentially cause a unique response by an individual microorganism. As many microorganisms may live and thrive in acidic environments, it is not sufficient to infer that a single organic acid useful against one microbe will provide the same utility against a different microbe. Such an error in extrapolation may be compounded by the fact that organic acids may impact on an organism by a variety of different mechanisms within the cell. Thus, the ordinary and straightforward problem encountered by *Kerkhoven* of using a detergent to treat a stain cannot be properly applied to the assortment of considerations necessary for inhibiting or killing a diverse spectrum of living organisms. As such, these substantial obstacles were overcome by the present invention, as provided by the patent application disclosure, which has painstakingly described the manner in which to make and use the appropriate combination of organic acids to inhibit or kill microbes.

As an additional matter, in *Kerkhoven*, there was no reason to expect that the combination of detergent compositions could act differently from the individual compositions comprising it. In essence, *Kerkhoven* stands for the proposition that green plus green equals greener. While green plus green may equal greener in the detergent arts, **the same cannot be said about the antimicrobial arts**. Moreover, one of skill in the art would not be able to use common sense to identify which organic acid combinations would be successful because each organic acid may provide subtle and different effects to the cell. In addition, the number of organic acid combinations that may reduce microbe viability is no small number, thus the proper combination cannot be easily tested or determined. The antimicrobial combinations of the present invention, per the

claim elements, have an intended physiological effect—they must be able to kill a variety of living microbes, and in particular, per claim 99, be able to kill mold. As such, the basic premise of *Kerkhoven*, i.e., green plus green equals more green, does not apply to antimicrobial organic acid combinations. In particular, it is not just the "acidity" of an organic acid that makes it kill microbes. Individual organic acids uniquely, and at times unpredictably, impact microbe cell growth, regulatory pathway, turgor pressure, and cell landscape.[12] Additionally, the degree of bioavailability (i.e., ability to reach the target microbe) varies for different organic acids, and different microbes are resistant to different pH ranges. In *Kerkhoven,* the compositions formed between the two detergents did not have to function in a physiological environment to be effective, and thus, was not accompanied by the same degree of unpredictability as in the present case. Notably absent from the art cited by the Office is any information from which it may be concluded that the recited organic acids of claim 99 would be beneficial when used together in combination; thus, unlike the situation in *Kerkhoven*, a person of ordinary skill would not have been motivated by the cited art to use the organic acids required in claim 99, in combination. As stated in MPEP § 2143, where there is no motivation to modify a reference as proposed, the proposed modification is not obvious.

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[12] Warnecke, T., and Gill, R., Microbial Cell Factories (2005) 4:25, a copy of this is attached hereto. For example, see the third page, column two of the article, which states:
Organic acid anions affect cell growth in a variety of manners. Increased anion concentration has been shown to lead to an increased transport of potassium ions into the cell, which increases turgor pressure [47,48]. To maintain a constant turgor pressure and cell volume, glutamate is transported out of the cell [48]. This transport activity concomitantly disrupts the osmolarity of the cytoplasm, which in turn lowers the cell's growth potential and viability. In addition to this general anion effect, **there are also effects specific to each organic acid.** It has been proposed that enzymes involved in protein synthesis are sensitive to a combination of two unrelated mechanisms, including the acidification of pHi and the formation of an anionic pool [35]. Although this finding implies that the **organic inhibition due to the anion pool could be acid specific**, the details describing this dual inhibition mechanism remain unclear. Kirkpatrick et al. reported proteins exhibiting increased expression in response to extracellular acetate [33]. Among these are the OppA transporter, RpoS regulon, several amino acid uptake proteins, DNA binding proteins, and extreme-acid preiplasmic chaperones. Interestingly, when formate was introduced in place of acetate the expression of the previously mentioned proteins was repressed, **indicating that the response was anion specific**. This finding introduces new challenges in addressing organic acid tolerance. Specifically, it highlights the need to engineer both pH and as well as specific anion tolerance into host organisms. (Emphasis added).

Even assuming, *arguendo*, that a *prima facie* case of obviousness has been established in view of the cited art, this case can be rebutted by showing that the claimed organic acid antimicrobial combinations of claim 99 achieves unexpected results. The claimed combinations, in fact, do provide unexpected results. As stated by Dr. Christopher Knight in his Declaration:

> … [w]e have research data, that in my opinion, demonstrates surprising and unexpected results for organic acid formulations falling within the scope of the '434 patent claims. As an example, attached to this Declaration is a graph (identified as figure 7) that depicts a synergistic effect for two organic acid formulations of the claimed invention. With reference to the attached graph, data is depicted for the antimicrobial activity of five different organic acid compositions against *Salmonella* in feed. The five organic acid compositions include: (1) 0.45% HMTBA alone (i.e., 2-hydroxy-4-(methylthio)butanoic acid, which is a compound of Formula (I) in the '434 application); (2) 0.45% butyric acid alone; (3) 0.45% lactic acid alone; (4) blend OA 4, which is 0.15% lactic acid, 0.15% propionic acid, and 0.15% HMTBA; and (5) blend OA 6, which is 0.1% lactic acid, 0.1% butyric acid, 0.1% propionic acid, and 0.15% HMTBA. The antimicrobial experiments were conducted in accordance with Novus's standard protocol entitled "low pH in Feed Test Procedure," a copy of which is attached to this Declaration. As depicted in the graph, the antimicrobial activity of either blend OA 4 or blend OA 6 achieved significantly higher killing of *Salmonella* at lower concentrations than could be achieved with any of the single organic acids alone.[13]

Stated another way, if the data depicted in Figure 7 aren't expressed in cfu, but rather in actual number of colonies killed, the result is even more striking. Blend OA 4 and Blend OA 6 have approximately a 10-fold improvement compared to any of the single organic acid compositions tested.

Because the references relied on by the Office do not disclose or suggest the presently claimed method for inhibiting mold by using the recited antimicrobial combinations, the Office appears to be applying "hindsight

[13] 37 C.F.R 1.132 Declaration of Dr. Christopher Knight, at paragraph 4, a copy of which is submitted herewith.

reconstruction" by using the teaching of the Applicants' patent application as a guide for searching, and analyzing the references in the right way to arrive at the claims at issue.[14] Such hindsight reconstruction is clearly contrary to the law.[15] The Office has simply not set-forth any sufficient art-based rationale as to why a person of skill in the art would have been motivated to modify the organic acid composition as taught by Doerr et al. (i.e., hydroxyl-methylthio butanoic acid), and combine it with the organic acid composition as taught by Rolow et al. (i.e., propionic acid), or combine both with other organic acids generally known in the art to arrive at the organic acid combination recited in claim 99. The mere identification in the prior art of each component of a composition **does not** show that the combination as a whole is obvious.[16] Rather, to establish a *prima facie* case of obviousness based on a combination of elements in the prior art, the law requires a motivation to select the references and **to combine them in the particular claimed manner to reach the claimed invention**.[17] Without this demonstration of the requisite motivation to make the Office's proposed modification, a *prima facie* case of obvious has not been established.

In view of the foregoing, the Applicants respectfully request withdrawal of the obviousness rejection of claim 99. Claims 100 to 103, which depend from claim 99, are likewise not obvious in view of the cited art for the reasons provided with respect to claim 99.

(c) Claims 88-89 are not rendered obvious by the cited art

Reconsideration is requested of the rejection of claims 88 and 89 under 35 U.S.C. 103 (a) in view of the '686 patent, the '053 patent, and in further view of Pinski et al. ('737 application)[18].

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[14] See *Orthopedic Equipment Co. v. United States*, 217 U.S.P.Q 193 (Fed. Cir. 1983).
[15] See *In re Dow Chemical*, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988).
[16] *In re Kahn*, 441 F.3d 977, 986 (Fed. Cir. 2006) (citing *In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998)).
[17] *Id.*
[18] US Publication No. 2002/0172737.

The '686 patent discloses a feed ration that among other ingredients has Alimet® (i.e., 2-hydroxy-4-(methylthio)butanoic acid), propionic acid, and citric acid.[19] The '053 patent discloses that 2-hydroxy-4-(methylthio)butanoic acid has antimicrobial activity.[20] Pinski et al. is said to disclose an aquatic foodstuff having an antimicrobial selected from "propionic acid, salt of propionic acid, citric acid or salt thereof."

The cited art-when taken singly or collectively-does not disclose all of the limitations of claim 88. Claim 88 requires use of an antimicrobial composition having minimally three separate organic acids. Namely, claim 88 requires **at least two organic acids** selected from the group **consisting of** formic acid, butyric acid, fumaric acid, lactic acid, benzoic acid, and propionic acid; and a third organic acid that is a compound of formula (I). The cited art doesn't disclose or suggest this combination. Moreover, for all of the reasons detailed in III(b), a person of ordinary skill would not have been motivated by the cited art to use the organic acids required in claim 88, in combination. Also, as demonstrated by the Declaration of Dr. Christopher Knight, the claimed organic acid antimicrobial combinations of claim 88 achieve unexpected results.

In view of the foregoing, the Applicants respectfully request withdrawal of the obviousness rejection of claim 88. Claim 89, which depends from claim 88, is likewise not obvious in view of the cited art for the reasons provided with respect to claim 88.

(d) Claims 86-87, and 91 are not rendered obvious by the cited art

Reconsideration is requested of the rejection of claims 86-87, and 91 under 35 U.S.C. 103 (a) in view of the '686 patent, the '053 patent, and in further view of Bland et al. ('467 patent)[21].

The '686 patent and '053 patent are discussed above. Resort to the '467 patent does not cure the defect in the Office's obviousness case. The '467

[19] '686 patent at column 7.
[20] '053 patent at column 1.
[21] U.S. Patent No. 5,591,467.

patent teaches the **benefit of formaldehyde** as a feed additive and provides a spray method for applying formaldehyde to the feed. Nowhere does the '467 patent disclose or suggest the antimicrobial combination of claim 86, which requires **at least two organic acids** selected from the group **consisting of** formic acid, butyric acid, fumaric acid, lactic acid, benzoic acid, and propionic acid; and a third organic acid that is a compound of formula (I).

If anything, in fact, the '467 patent teaches away from the antimicrobial organic acid combination recited by claim 86. The '467 patent specifically recites:

> …[i]t is now generally recognized that limiting the introduction of Salmonella through the feed is the most effective long range plan for improving the situation and many compounds with known bacteriocidal properties, such as lactic acid, propionic acid, formic acid, butyric acid, sorbic acid, benzoic acid and combinations of these have been tested. While many of these agents kill bacteria in solution, they do not kill all bacteria in animal feed stuffs.[22]

In view of this passage, a skilled artisan would not be motivated to use any of the disclosed organic acids in combination to prevent microbial growth in feed-as required in the presently pending claims-because per the '467 patent the organic acid are bacteriocidal in vitro but "they do not kill all bacteria in animal feed stuffs." The whole point of the present invention is antimicrobial combinations that kill microbes in feed or water.

Additionally, for all of the reasons detailed in III(b), a person of ordinary skill would not have been motivated by the cited art to use the organic acids required in claim 86, in combination. Moreover, as demonstrated by the Declaration of Dr. Christopher Knight, the claimed organic acid antimicrobial combinations of claim 86 achieve unexpected results.

In view of the foregoing, the Applicants respectfully request withdrawal of the obviousness rejection of claim 86. Claims 87 and 91, which depend from

[22] '467 patent, at column 2, lines 18 to 26.

claim 86, are likewise not obvious in view of the cited art for the reasons provided with respect to claim 86.

(e) Claims 94-95 are not rendered obvious by the cited art

Reconsideration is requested of the rejection of claims 94 and 95 under 35 U.S.C. 103 (a) in view of the '686 patent, the '053 patent, and in further view of Friedman et al. ('208 patent)[23].

The '686 patent and '053 patent are discussed above. Resort to the '208 patent does not cure the defect in the Office's obviousness case. Per the Office, the '208 patent is said to disclose the use of antimicrobial agents in pet foods. Nowhere, however, does the cited art-either singly or collectively-disclose or suggest the use of the specific antimicrobial agent required by claim 94.

For all of the reasons detailed in III(b), a person of ordinary skill would not have been motivated by the cited art to use the organic acids required in claim 94, in combination. Moreover, as demonstrated by the Declaration of Dr. Christopher Knight, the claimed organic acid antimicrobial combinations of claim 94 achieve unexpected results.

In view of the foregoing, the Applicants respectfully request withdrawal of the obviousness rejection of claim 94. Claim 94, which depends from claim 95, is likewise not obvious in view of the cited art for the reasons provided with respect to claim 94.

IV. Conclusion

In light of the foregoing, the Applicants request entry of the amendments to the claims, withdrawal of the claim rejections, and solicit an allowance of all pending claims.

[23] U.S. Patent No. 4,495,208.

The Commissioner is hereby authorized to change any and all fees that may be required or credit any overpayment to Deposit Account No. 50-1662.

POLSINELLI SHALTON FLANIGAN SUELTHAUS PC

Respectfully submitted,

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